PB90-130683

Integrated Quantitative Cancer Risk Assessment of Inorganic Arsenic

(U.S.) Environmental Protection Agency, Washington, DC

Feb 89

U.S. Department of Commerce
National Technical Information Service
NTIS

United States
Environmental Protection
Agency

PB90-130683
OHEA-C-312
February 1989
FINAL

EPA/600/D-89/193

Research and Development

INTEGRATED QUANTITATIVE CANCER RISK ASSESSMENT

OF INORGANIC ARSENIC

Prepared for

Presentation at the Symposium
on Health Risk Assessment
Tapei, Taiwan
December 20-22, 1988

Prepared by

Human Health Assessment Group
Office of Health and
Environmental Assessment
Washington DC 20460

REPRODUCED BY
U.S. DEPARTMENT OF COMMERCE
NATIONAL TECHNICAL INFORMATION SERVICE
SPRINGFIELD, VA. 22161

TECHNICAL REPORT DATA
(Please read Instructions on the reverse before completing)

1. REPORT NO.	2.	3. RECIPIENT'S ACCESSION NO.
EPA/600/D-89/193		PB90 130683/AS

4. TITLE AND SUBTITLE	5. REPORT DATE
INTEGRATED QUANTITATIVE CANCER RISK ASSESSMENT OF INORGANIC ARSENIC	February 1989
	6. PERFORMING ORGANIZATION CODE: EPA/600/021
7. AUTHOR(S): Chao W. Chen and Chien-Jen Chen	8. PERFORMING ORGANIZATION REPORT NO.: OHEA-C-312
9. PERFORMING ORGANIZATION NAME AND ADDRESS: Office of Health and Environmental Assessment, Human Health Assessment Group, U.S. Environmental Protection Agency, Washington, DC 20460	10. PROGRAM ELEMENT NO.
	11. CONTRACT/GRANT NO.
12. SPONSORING AGENCY NAME AND ADDRESS	13. TYPE OF REPORT AND PERIOD COVERED: Symposium Paper
	14. SPONSORING AGENCY CODE: EPA-600/21

15. SUPPLEMENTARY NOTES
Presentation at the Symposium on Health Risk Assessment
Tapei, Taiwan December 20-22, 1988

16. ABSTRACT

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17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group

18. DISTRIBUTION STATEMENT	19. SECURITY CLASS *(This Report)*	21. NO. OF PAGES
Release to public	Unclassified	24
	20. SECURITY CLASS *(This page)* Unclassified	22. PRICE

EPA Form 2220-1 (Rev. 4-77) PREVIOUS EDITION IS OBSOLETE

INTEGRATED QUANTITATIVE CANCER RISK ASSESSMENT OF INORGANIC ARSENIC

Chao W. Chen
U.S. Environmental Protection Agency
Washington, D.C., USA

and

Chien-Jen Chen
Academia Sinica, Taiwan
Republic of China

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ABSTRACT

This paper attempts to make an integrated risk assessment of arsenic, using data on humans exposed to arsenic via inhalation and ingestion. The data useful for making an integrated analysis and data gaps are discussed. Arsenic provides a rare opportunity to compare the cancer risk to humans due to exposure to a metal carcinogen via inhalation and ingestion. Our assessment suggests that the elevated lung cancer mortality observed in the population of the blackfoot disease endemic areas is consistent with that observed in copper smelter workers who, presumably, were exposed to arsenic via inhalation. We also speculate, on the basis of overall information on arsenic, that smelter workers could have an elevated cancer mortality in sites other than the lung, contrary to the usual assumption that lung tissue is the only target tissue for cancer when exposure is via inhalation.

INTRODUCTION

Inorganic arsenic has been found to be associated with cancer of several sites in humans exposed to arsenic via either inhalation or ingestion. The association between inhaled arsenic and lung cancer has long been established (U.S. EPA, 1985). Recently, arsenic in drinking water has also been found to be associated with several internal cancers, including cancer of the lung (Chen et al., 1985, 1986).

Arsenic provides a unique opportunity for studying the carcinogenic effect of metal carcinogens because of the availability of data on humans exposed to arsenic via ingestion and inhalation. A question that is often raised is whether or not a metal which is carcinogenic via inhalation should be considered carcinogenic via the oral route of exposure. The reason that such a question is raised for metal compounds but not for most of the other non-metal compounds is because the occupational exposure to metal compounds usually occurs in a manufacturing setting that generated a high dust concentration, and the observed carcinogenic effect may actually be due to the interaction of the compound and the inhaled particle that is deposited in the lung tissue.

The objective of this paper is to perform an integrated quantitative risk assessment of arsenic, using all the available data, including cancer data on humans exposed to arsenic via inhalation and drinking water and pharmacokinetic data in humans and animals. The advantage of doing an integrated risk assessment is that the risk estimate calculated from one data set can be compared with the estimate from another data set. For instance, some critics argue that data from the Taiwan studies are not applicable to the U.S. population because the population in the blackfoot disease (BFD)-endemic

areas had poor or protein-deficient diets. They argue that a protein-deficient diet will lower the methylation capacity of the liver, and when the exposure exceeds a certain level, the arsenic deposition in certain target tissues increases. One way to answer this question is to compare the arsenic potencies calculated from the Taiwan data with those calculated from other data bases.

DATA AVAILABLE FOR QUANTITATIVE RISK ASSESSMENT

1. DATA FROM DRINKING WATER

Almost all the studies that provide adequate data for risk calculations are those conducted on populations in the BFD-endemic areas in Taiwan. They were exposed to arsenic in the drinking water; arsenic concentrations ranged from 0.35 ppm to 1.14 ppm with a median of 0.78 ppm.

a. Skin cancer studies

The best dose-response data on skin cancer are from Tseng et al. (1968) and Tseng (1977). These studies (herein referred to as the Taiwan study) reported the results of a large (over 40,000 persons) prevalence study of persons living in the BFD-endemic areas. Four hundred and twenty-eight (428) skin cancers were found in the studied population, while none was found in a control population of 7,500 persons. Recently, these data have been used to estimate the skin cancer risk due to arsenic in drinking water (U.S. EPA, 1988).

b. Internal cancer studies

In a study of the population in the BFD-endemic areas in Taiwan, Chen et al. (1985) found that the standard mortality ratios (SMR) for cancers of lung, liver, kidney, bladder, colon, and skin were also significantly elevated. The

follow-up period of this cohort is from 1968 to 1982. In a recent study of the same cohort (Chen et al., 1988) with a follow-up period from 1973 to 1986, essentially the same results are found. These data (Chen et al., 1988), except for the colon and skin cancers, are used to calculate an additional internal cancer risk for arsenic. The colon cancer data are not used because there is no clear dose-response relationship. The skin cancer mortality data is not used because the fatality rate of skin cancer is lower than the internal cancers, and the record may not be as reliable.

2. DATA FROM INHALATION EXPOSURE

The association of inorganic arsenic with respiratory cancer has long been established among workers employed in copper smelters and pesticide plants (Lee and Fraumeni, 1969; Milham and Strong, 1974; Tokudome and Kuratsune, 1976; Pinto et al., 1977, 1978; Mabuchi et al., 1979; Enterline and Marsh, 1980, 1982; Lubin et al., 1981; Higgins et al., 1982; Lee-Feldstein, 1983; Enterline, 1987). In addition to respiratory cancer, digestive tract cancer has been found to be associated with arsenic exposure among smelter workers (Lee-Feldstein, 1983), however, the actual digestive tract cancer data are not available to us.

The studies that provide sufficient data for risk calculation are those prospective studies that were conducted on smelter workers in Anaconda, Montana (Brown and Chu, 1983a,b,c; Lee-Feldstein, 1983; Higgins et al., 1982) and in Tacoma, Washington (Enterline and Marsh, 1982).

The study of Lee-Feldstein (1983) reported on a cohort of 8,047 white males who were employed as smelter workers in Anaconda for a year or more before 1957 and whose mortality experience was observed from 1938 to 1977. The Lee-Feldstein study is an extension of the study by Lee and Fraumeni

(1969) with 14 years additional follow-up. Higgins et al. (1982) followed up with a sample of 1,800 men from the Anaconda smelter cohort originally studied by Lee and Fraumeni (1969) but used different exposure classifications and different methods of analysis. Using the Anaconda data reported by Lee-Feldstein, Brown and Chu (1983a,b,c) analyzed the effect of arsenic exposure on the stage of carcinogenesis, using the multistage theory of carcinogenesis (Whittemore, 1977).

The study of Enterline and Marsh (1982) included all men (2,802) employed at the Tacoma smelter for a year or more during 1940-1964, and their mortality experience was followed up to 1976. Recently, this cohort has been re-analyzed using urinary excretion as the exposure marker (Enterline, 1987).

METHODS FOR CALCULATING CARCINOGENIC RISK OF ARSENIC

In order to compare the carcinogenic risk of arsenic calculated from populations exposed to arsenic via inhalation and ingestion, the carcinogenic risk is calculated for each cancer site separately.

The model described below is used to calculate the cancer risks using data from Chen et al. (1988). For the skin cancer data from the Taiwan study and the lung cancer mortality data from the study of smelter workers, a similar but slightly modified model is used to accommodate the nature of data available. This model has been shown to arise from the multistep nature of carcinogenesis (Armitage and Doll, 1954; Whittemore and Keller, 1978). It has also been shown to arise from an epigenic hypothesis when the reversible cellular change is programmed to occur randomly (Watson, 1977). In the absence of a more specific mechanism of action, this model is considered adequate.

The age and cause-specific mortality rate, I(t,d), is assumed to have the following form

$$I(t,d) = B(t) + H(t,d)$$

where B(t) is the background mortality rate, and H(t,d) is the mortality rate due to the arsenic exposure at age, t, and dose rate, d. In this calculation, H(t,d) is assumed to have the mathematic form

$$H(t,d) = f(d)t^k$$

where $f(d) = ad + bd^2$ is found to be adequate when the data from Chen et al. (1988) is used; the parameters a, b, and k are estimated by the maximum likelihood method, assuming that the number of cancer deaths is a Poisson random variable with the mean equal to NI(t,d), where N is the person-years at risk. The probability of cancer by age t due to exposure to arsenic at dose d, P(t,d), taking into account the competing risk, is calculated by

$$P(t,d) = \int_0^t H(s,d)\exp(-[H(u,d) + A(u)]du)ds$$

where exp[-A(t)] is the probability of surviving up to age t for the general population for which the risk prediction is made. In actual calculation, exp[-A(t)] is assumed to be constant over a five-year interval as provided in the U.S. Vital Statistics. In order to compare risk estimates calculated from data derived from different populations, the U.S. population is used as the standard population for risk prediction.

RESULTS OF RISK CALCULATIONS

1.— DRINKING WATER--INTERNAL CANCER MORTALITIES

Table 1 presents the lifetime risk per 1 ug/kg per day of arsenic intake from the drinking water. These results are calculated on the basis of data from Chen et al. (1988) and will be evaluated, against other data bases, for their reasonableness. In these calculations, assumptions are made that a male weighs 55 kg and drinks 3.5 liters of water per day; a female weighs 50 kg and drinks 2 liters of water per day.

The risk estimates given in Table 1 may be somewhat underestimated because it is assumed that the arsenic intake for each person continues from

TABLE 1. LIFETIME RISK DUE TO 1 ug/kg PER DAY OF ARSENIC INTAKE AND THE MAXIMUM LIKELIHOOD ESTIMATE (MLE) OF PARAMETERS IN THE FUNCTION H(t,d)[a]

Data Base	Lifetime Risk per (ug/kg/day)	MLE of parameters		
		a	b	k
Lung/male	2.1×10^{-3}	1.87×10^{-12}	4.63×10^{-18}	4.16
Lung/female	2.6×10^{-3}	7.93×10^{-11}	9.81×10^{-24}	3.32
Liver/male	9.9×10^{-4}	1.03×10^{-12}	4.29×10^{-17}	3.02
Liver/female	6.7×10^{-4}	6.38×10^{-11}	2.12×10^{-14}	3.04
Kidney/male	5.2×10^{-4}	8.04×10^{-13}	1.40×10^{-29}	4.03
Kidney/female	9.2×10^{-4}	1.26×10^{-12}	2.63×10^{-15}	4.06
Bladder/male	1.8×10^{-3}	1.78×10^{-12}	9.89×10^{-18}	4.14
Bladder/Female	3.3×10^{-3}	7.82×10^{-14}	6.46×10^{-27}	5.02

[a] t is age in years, and d is the arsenic intake in ug/kg/day.

birth to the end of follow-up during 1973-1986. Since tap water became available to most residents of the endemic areas in 1966, residents in these areas may no longer be exposed to arsenic through drinking water after 1966. A reasonable estimate is that in the last 10 years before the termination of follow-up, the studied population is no longer exposed to arsenic through drinking water. If the latent period of the cancers at issue is greater than 10 years, then the underestimation is not expected to be significant. However, this assumption may not be valid if arsenic stimulates the proliferation of the existing pre-neoplastic cells or the progression of pre-neoplastic cells into malignant cells. If arsenic acts in such a manner, then the probability of cancer is greater for older persons, who are likely to possess more pre-neoplastic cells than younger persons. There is some experimental evidence showing this may be the case for some type of cells (Lee et al., 1986). The best data for evaluating this hypothesis are the cancer mortality experience of migrants who moved in and out of the BFD-endemic areas. More precise exposure information on individual persons in the cohort will also be needed to resolve this issue.

On the other hand, the risk may be somewhat overestimated because the (inorganic) arsenic intake from sources other than drinking water is not included in the calculations. Information on inorganic arsenic intake from other sources is needed to make a meaningful adjustment.

2. INHALATION--LUNG CANCER MORTALITY

Using data from Brown and Chu (1983a,b,c), Lee-Feldstein (1983), Higgins et al. (1982), and Enterline and Marsh (1982), the lifetime risk due to

1 ug/m^3 of arsenic in air is calculated to range from $1.3x10^{-3}$ to $6.8x10^{-3}$ (Table 2).

3. DRINKING WATER--SKIN CANCER

Recently, the issues and quantitation of the arsenic-induced skin cancer risk has been extensively evaluated and reported in the U.S. Environmental Protection Agency's Special Report on Ingested Inorganic Arsenic (1988). On the basis of skin cancer prevalence data reported in the Taiwan study, the lifetime risk of skin cancer due to 1 ug/kg per day of arsenic intake is estimated to range from $1.0x10^{-3}$ to $2.0x10^{-3}$ (U.S. EPA, 1988). This estimate has been found, in the U.S. EPA report, to be comparable to the experience of the Mexican population reported in Cebrian et al. (1983).

EVALUATION OF TAIWAN-BASED CANCER RISK ESTIMATES

To compare carcinogenic risk calculated on the basis of different data bases, the risk to a standard person must be calculated. We assume that a standard person weighs 70 kg, drinks 2 liters of water and inhales 20 cubic meters of air per day. The population of standard persons is assumed to have the same age distribution and life expectancy as the U.S. population (males and females combined). The carcinogenic risk (potency) is defined as the incremental (over background) lifetime probability of developing cancer to a standard person due to an intake of 1 ug/kg per day of arsenic.

1. COMPARISON AMONG WATER-BASED ESTIMATES--INTERNAL CANCERS

As shown in Table 1, for each cancer site, the risks for males and females are practically identical, all within twofold of magnitude, indicating no sex difference in the carcinogenic response. Furthermore, the carcinogenic

TABLE 2. LIFETIME RISK DUE TO 1 ug/m^3 (UNIT RISK) OF ARSENIC IN THE AMBIENT AIR

Exposure Source	Study	Unit Risk (Risk per ug/m^3)	Crude Risk Estimate[a] Per 1 ug/kg/day intake from air
Anaconda, Montana	Brown & Chu	1.3×10^{-3}	4.6×10^{-3}
	Lee-Feldstein	2.8×10^{-3}	9.8×10^{-3}
	Higgins	4.9×10^{-3}	1.7×10^{-2}
Tacoma, Washington	Enterline & Marsh	6.8×10^{-3}	2.4×10^{-2}

[a]Assume a person weighs 70 kg and inhales 20 m^3 of air per day with 100% absorption. Thus, 1 ug/m^3 of arsenic in air is equivalent to 0.285 ug/kg/day of arsenic intake. Crude risk = Unit Risk/0.285.

SOURCE: U.S. EPA (1984).

risks are comparable among four different organs. This is very interesting because the observation is supported by pharmacokinetic data in animals which show arsenic concentrations in lung, liver, and kidney tissues are comparable by either inhalation (Bencko and Symon, 1970; Rozenshtein, 1970) or oral exposure (Vahter and Norin, 1980). Although the tissue concentration in the bladder is not reported, it is known that urine excretion is the major route of arsenic elimination when it is taken orally or by inhalation, and thus, one would expect the bladder to be a target organ of arsenic assault. Pomroy et al. (1980) conducted an experiment on six volunteers and found that about 62% (mean 62.3% and standard deviation 4%) of arsenic was excreted in urine 7 days after a single oral dose of arsenic. Buchet et al. (1981a,b) also experimented on human volunteers and found that about 60% of arsenic was excreted in urine at the fifth day, 5 days after repeated oral doses of sodium

arsenite (125-1000 ug per day). In their epidemiologic study of smelter workers, Pinto et al. (1977) found that arsenic in urinary excretion is a reliable exposure marker, indicating that urinary excretion may be a major route of elimination when exposed via inhalation.

Tables 3-5 give the tissue concentrations in different organs after inhalation and oral ingestion. Data in these tables demonstrate that the lung, liver, and kidney have comparable tissue concentrations over time after oral or inhalation exposure. The lack of data prevents us from constructing a physiologically based pharmacokinetic (PBPK) model. A PBPK model would be very useful for predicting the fate of arsenic in the body across species lines and routes of exposure.

2. COMPARISON BETWEEN WATER AND AIR-BASED RISK ESTIMATES--LUNG CANCER

The lung cancer risk estimates calculated on the basis of inhalation data ranges from 1.3×10^{-3} to 6.8×10^{-3} per ug/m^3 or, in terms of crude estimates, from 4.6×10^{-3} to 2.4×10^{-2} per ug/kg per day (Table 2) while the lung cancer risk has values 2.1×10^{-3} and 2.6×10^{-3} per ug/kg per day, calculated respectively, on the basis of male and female drinking water data (Table 4). The water-based risk estimate is about 2 to 10 times smaller than the crude air-based risk estimate. This difference is reasonable because, for a given body dose of 1 ug/kg per day, more arsenic reaches lung tissue after inhalation than after oral exposure. Furthermore, part of the difference may be due to the difference of the valence states of arsenic: occupational exposure of arsenic is more likely to be in the trivalent form while the drinking water exposure is more likely to be in the pentavalent form.

TABLE 3. TISSUE CONCENTRATION (ug/g WET TISSUE) IN HAIRLESS MICE AFTER INHALATION EXPOSURE TO ARSENIC TRIOXIDE, 179 ug/m^3 OF ARSENIC, 6 HOURS PER DAY, 5 DAYS PER WEEK

Duration of Exposure (weeks)	Liver	Kidney
1	0.30	0.32
2	0.74	0.91
4	0.06	0.12
6	0.07	0.12

SOURCE: Bencko and Symon (1970).

TABLE 4. TISSUE CONCENTRATION (ug/g WET TISSUE) IN FEMALE ALBINO RATS AFTER INHALATION EXPOSURE TO ARSENIC TRIOXIDE 24 HOURS PER DAY FOR 3 MONTHS

Exposure Concentration (ug/m^3)	Liver	Lung
60.7	2.09	2.07
4.9	0.61	0.62
1.3	0.37	0.41
0.0	0.36	0.38

SOURCE: Rozenshtein (1970).

TABLE 5. ARSENIC CONCENTRATION (ug/g WET TISSUE) IN ORGAN OF MICE 2 HOURS AND 24 HOURS AFTER A SINGLE ORAL DOSE (4 mg/kg) OF ^{74}As-LABELED ARSENITE AND ARSENATE

	2 hours		24 hours	
	Liver	Kidney	Liver	Kidney
Arsenate	3.52	8.73	0.04	0.06
Arsenite	6.72	7.44	0.39	0.78

SOURCE: Vahter and Norin (1980).

3. TAIWAN-BASED SKIN CANCER RISK ESTIMATE AND U.S. EXPERIENCE

As discussed before, the experience in both Taiwan and Mexico are very similar with respect to the dose-response of skin cancer prevalence. However, both of the studied populations suffer from poor nutritional intake. Therefore, it is desirable to compare the Taiwan-based risk estimate with the experience of the U.S. population. So far, the effort has been toward showing that all the studies on U.S. population lack the statistical power to detect the cancer response, using the Taiwan-based risk estimate calculated by the EPA in 1984 (Andelman and Barnett, 1983). Since the new EPA (1988) risk estimate of the skin cancer is about 10 times smaller than the previous value, the conclusion that all the U.S. studies lack the statistical power still holds.

In this section, it is shown that the Taiwan-based risk estimate appears reasonable, using the hyperkeratosis incidence observed in a small community study in the U.S. (Southwick et al., 1981) and the observation in Tseng et al. (1968) that about 11% of persons with keratosis also had skin cancer. In

Tseng et al. (1968), 309 persons were observed with both skin cancer and keratoses while 2,868 persons were observed with keratoses. A direct comparison of keratosis prevalence between the U.S. and Taiwan populations is not possible because the age-specific prevalence rate in the Taiwan population, which is required for the risk calculation, is not available.

About 150 qualified residents from three communities (Delta, Hinckley, and Deseret) in Millard County, Utah, participated in the Southwick study. Males and females who were 5 years of age or older and were current residents of Hinckley or Deseret for at least 5 years were selected to participate in the study. All qualified individuals were included in the study, except for a few who refused the invitation to participate. The median arsenic intake from the drinking water for these residents was estimated to be 7.3 ug/kg per day. Control participants were selected from residents of Delta where drinking water contains less than 25 ug/liter of arsenic. The median arsenic intake from these residents was estimated to be 0.73 ug/kg per day. The study participants came from a homogeneous, stable population with minimum influence from cigarette smoking and alcohol, due to the predominantly Mormon lifestyle of the Millard County residents. Most of the participants were life-long residents of their community. Table 6 gives the prevalence of hyperkeratoses and exposure information on control and exposed communities.

Some of the residents in the control community were actually exposed to higher arsenic doses than many of the residents in the exposed community. For the purpose of dose-response modeling, it would be more meaningful to classify the participants into exposure groups according to the level of exposure, rather than by the community boundary. However, such information is not available to us.

Applying the same model as that used for the internal cancers (but with a linear dose term and the assumption of the binomial distribution) to the Utah data in Table 6, the risk of keratoses is calculated to be 1.4×10^{-2} per ug/kg per day. Thus, the risk of skin cancer would be 1.5×10^{-3} per ug/kg per day if it is assumed that 11% of persons with keratoses will eventually also have skin cancer as observed in Taiwan. This risk projection is similar to that derived from the Taiwan study, indicating the comparability of both Taiwan and the U.S. experiences.

CONCLUSIONS

Our overall evaluation of the total data base on arsenic compounds suggests the following:

1. The elevated lung cancer mortality observed in the Taiwanese population exposed to arsenic via drinking water is consistent with that observed in the smelter workers who were, presumably, exposed to arsenic via inhalation.

2. The incremental risk of skin cancer and death from internal cancers (lung, liver, bladder) due to arsenic appear to be comparable between males and females, lending further support to the validity of the study results on the BFD-endemic areas.

3. The skin cancer potential of arsenic via drinking water appears consistent among data from Taiwan, Mexico, and the U.S. (U.S. EPA, 1988).

4. On the basis of pharmacokinetic data in animals and elevated mortality of internal cancers in humans exposed to arsenic via drinking water,

TABLE 6. PREVALENCE OF KERATOSES IN CONTROL (DELTA) AND EXPOSED (HINCKLEY AND DESERET) COMMUNITIES

Age	Control (0.73 ug/kg/day)	Exposed (7.3 ug/kg/day)
7 - 20	0/25	0/42
21 - 40	0/31	3/29
41 - 60	1/31[a]	1/43
61 and over	1/61	3/31

[a]One person with keratosis in this group is not included because he was exposed to 5.3 ug/kg/day of arsenic, which is more than 7 times greater than the control dose of 0.73 ug/kg/day.it seems reasonable to speculate that arsenic in ambient air could also induce cancer in sites other than the lung.

DISCUSSION

In this paper, we attempt to integrate all the available information on arsenic into a single risk assessment, be it exposure via inhalation or via drinking water. To a certain extent, this objective is accomplished. As we are aware, this is the first attempt to integrate and compare differing exposure pathways for a metal, incorporating cancer response and phamacokinetic data. This integrated assessment not only reinforces the results from studies on the population in the BFD-endemic areas, it also leads to the interesting speculation that arsenic in ambient air may also induce cancer in sites other than the lung.

It is inevitable that any risk assessment is associated with uncertainties because of a lack of data. The data not now available but obtainable and probably useful for improving the risk assessment of arsenic

include the epidemiologic study on migrants who moved into and out of the BFD-endemic areas, and pharmacokinetic parameters (e.g., partition coefficients of tissues and blood, tissue concentrations over time) for constructing a physiologically based pharmacokinetic model. Of utmost importance, however, is the understanding of the mechanism of action. From the viewpoint of environmental hazard prevention and the dose-response modeling, the identification of the stage(s) in the multistep carcinogenesis model that is affected by arsenic is the most important task. This information can be derived from a basic mechanism study on animals and the epidemiologic study on migrants.

Acknowledgment: We are grateful to Herman Gibb for his discussion and review of the draft during the preparation of this paper.

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